Clinician Brief

Evidence, interactions and safety

- **For prescribers, pharmacists and mental health clinicians**

Open-source harm-reduction framework. Not medical advice. Use alongside clinical care.

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> **In this chapter.** A short summary for prescribers, pharmacists, and mental health clinicians

1. Plain statement on evidence and projections

- **The Kernel’s outcome numbers are projections.** Craving-reduction ranges, 1-10 “before and after” scores, and timeline expectations come from the Kernel’s own framework. They are not trial results, have no published methodology or control group, and should not be used for prognosis or to set patient expectations.
- **The Kernel is a framework, not a treatment with proven efficacy.** Its premise, that treatment-resistant addiction is frequently driven by testable genetic variants that standard care misses, is a hypothesis.
- **It should sit beside, not replace, evidence-based care.** Medicines for opioid use disorder (buprenorphine, methadone, extended-release naltrexone), pharmacotherapy for alcohol use disorder, contingency management, and psychotherapy have established evidence. Kernel timelines must not delay, substitute for, or end these.
- **Evidence tiers used here.** **[Established]** widely accepted clinical fact. **[Emerging]** plausible, limited or mixed evidence. **[Kernel hypothesis]** the framework’s own claim or projection, not trial-tested. Where no tier is shown, the text is a practical note.

The patient has been told the Kernel is “a set of questions and hypotheses to explore with you,” not a substitute for your judgment.

2. What your patient may bring

Item	What it is	How to treat it
Estimated "Kernel Code" and profile (for example "Depleted Worrier")	A code from a self-report questionnaire	**[Kernel hypothesis]** Unvalidated. It is not a genotype. Ask for actual test reports.
Wallet "safety card" Item	Estimated or confirmed profile, any CYP2D6 or other results, an "avoid" list What it is	Verify against a clinical report. The example "avoid folic acid" is a Kernel How to treat it hypothesis (see section 4).
Medication and supplement list	Everything they take	Use it for interaction review. This is the most useful item.
Weekly tracker	Mood, energy, sleep, anxiety, craving, clarity (1-10), optional homocysteine and B12	Patient-reported; useful as a trend.

3. The seven genetic systems and what supports them

The Kernel organizes its model around seven genes. In every case, the link to addiction or to a "personality type" is the framework's own hypothesis.

Gene	Clinical role	Kernel claim	Evidence tier
MTHFR (C677T, A1298C)	Folate metabolism	Variants lower dopamine/serotonin baseline, and substances compensate	Reduced enzyme activity and modestly raised homocysteine: **[Established]**. Link to addiction and to a "depleted" phenotype: **[Kernel hypothesis]**. Professional guidance (for example ACMG) advises against routine MTHFR genotyping for most clinical questions.

Gene	Clinical role	Kernel claim	Evidence tier
COMT Val158Met Gene	Catecholamine clearance in prefrontal cortex Clinical role	Val/Val "Warrior" seeks stimulants; Met/Met "Worrier" seeks depressants Kernel claim	Enzyme activity difference: **[Established]**. Substance-type prediction: **[Kernel hypothesis]**; the literature is mixed. CPIC reviewed COMT for opioid prescribing and made no recommendation (verify current status). Not an Evidence tier actionable genotype for antidepressant or exercise prescribing.
CYP2D6	Metabolizes many opioids and antidepressants	Poor metabolizers get no effect from prodrugs; ultra-rapid metabolizers risk toxicity	**[Established]** CPIC and FDA-labeled guidance exists for codeine, tramadol, and many antidepressants. This is the strongest part of the framework.
CYP3A4/5	Metabolizes about half of drugs, including fentanyl and many benzodiazepines	Interaction collisions; grapefruit inhibition	Interactions and grapefruit: **[Established]**. Genotyping is rarely actionable; interaction review is.
GABRA2 / GABRB3	GABA-A receptor subunits	High-risk variants: impaired impulse control, faster alcohol or benzodiazepine dependence, higher withdrawal seizure risk	Association with alcohol dependence: **[Emerging]**, with inconsistent replication. Seizure prediction: **[Kernel hypothesis]**. Assess withdrawal risk clinically (prior seizures or delirium, quantity, duration, co-use). No genotype changes the need for supervision.
OPRM1 A118G	Mu-opioid receptor	G allele needs higher opioid doses and responds better to naltrexone	**[Emerging]**, mixed. CPIC reviewed OPRM1 for opioids and made no recommendation.

Gene	Clinical role	Kernel claim	Evidence tier
DRD2 Taq1A (located in the ANKK1 gene) Gene	Linked to D2 receptor A1 allele reduces density Clinical role	receptors (about 30%) and causes “reward deficiency syndrome” Kernel claim	Imaging associations: [Emerging], contested. “Reward deficiency syndrome” as a unifying Evidence tier construct: **[Kernel hypothesis]**.

Population “Warrior/Worrier” labels are descriptive shorthand. They are not diagnoses and should not be recorded as genotype-derived findings.

4. Labs and supplements the patient may be following

The Kernel’s own materials list amounts. **This brief omits all supplement doses. Dose per prescriber and pharmacist.** The Kernel states these are “mechanism-based, not addiction- specific clinical trial evidence.” Please consider that statement the most accurate description of the evidence.

4.1 Labs the Kernel suggests

Test	Evidence tier and note
Homocysteine	[Established] as a lab test; as an MTHFR “proxy,” [Emerging]. Kernel target under 10 umol/L is [Kernel hypothesis]; use your lab’s reference range.
Vitamin B12	[Established] for diagnosing deficiency. Kernel target above 400 pg/mL is **[Kernel hypothesis]**.
Vitamin D (25-OH)	[Established] for deficiency. Kernel’s target range is [Kernel hypothesis].
CYP2D6 genotype	[Established] utility for codeine, tramadol, and several psychotropics (CPIC). Commercial panels vary; confirm interpretation against CPIC and FDA labeling.
MTHFR genotype	[Established] that it can be run; **[Kernel hypothesis]** that it should guide supplement choice (see above).
COMT genotype	[Kernel hypothesis] for prescribing; limited clinical actionability.
GABRA2/GABRB3	[Kernel hypothesis] for withdrawal risk. Do not use in place of clinical assessment.

4.2 Supplements, evidence tiers, and interaction cautions

Supplement	Evidence tier	Interaction and safety cautions to keep
L-methylfolate (the Kernel favors it over folic acid) Supplement	Adjunct use in depression: [Emerging], mixed. Benefit Evidence tier for addiction: **[Kernel hypothesis]**.	Titrate under supervision: reports of anxiety, insomnia, Interaction and safety cautions to keep and agitation at higher exposure ([Emerging], case-level). Kernel's claim that folic acid "worsens methylation" in T/T patients is a [Kernel hypothesis]; do not stop folic acid in pregnancy or preconception on this basis.
Methylcobalamin (B12)	Treatment of deficiency: [Established]. Benefit without deficiency: [Emerging], limited.	Monitor levels.
Magnesium (glycinate)	Anxiety or sleep: [Emerging], limited.	Caution in renal impairment. May add to antihypertensive effects.
L-theanine	Stress or sleep: [Emerging], small studies.	Additive sedation with benzodiazepines or other sedatives is possible: monitor.
L-tyrosine	Dopamine support in recovery: **[Kernel hypothesis]**	Contraindicated with MAOIs. Caution with thyroid disease. Do not combine with levodopa. Avoid during active stimulant use and in active psychosis. May worsen psychotic symptoms; wait for psychiatric clearance.
N-acetylcysteine (NAC)	Craving reduction: [Emerging], promising but inconsistent (for example, cannabis use disorder: positive in adolescents, not in Control or the ED first, not to a larger adult trial). The established use is acetaminophen overdose.	Caution with nitroglycerin (headache, hypotension). Suspected acetaminophen overdose: route to Poison oral supplements.
SAMe Supplement	Depression, adjunct: [Emerging]. Evidence tier	Contraindicated in bipolar disorder without a mood stabilizer (can precipitate hypomania or mania). Avoid Interaction and safety cautions to keep with MAOIs. Theoretical serotonin-syndrome risk with other serotonergic drugs.

Supplement	Evidence tier	Interaction and safety cautions to keep
Omega-3 (EPA/DHA)	Depression, adjunct: **[Emerging]**.	Modest anti-clotting effect at higher intakes: notify the prescriber if the patient is on warfarin or other anticoagulants.
Taurine	**[Kernel hypothesis]**; limited human data.	Generally well tolerated; limited interaction data.
5-HTP (appears elsewhere in Kernel materials)	**[Emerging]**, weak.	Only on physician advice. Never with serotonergic drugs (SSRIs, SNRIs, MAOIs, tramadol, MDMA, and similar). Kernel materials give inconsistent timing guidance after serotonergic substance use, so the cautious rule is physician confirmation.
Research peptides (for example BPC-157, Selank, Semax, Epitalon) mentioned elsewhere in the Kernel	**[Kernel hypothesis]** Not approved for these uses; not recommended.	Unregulated products; quality and safety unknown. Ask directly if the patient is using any.

Interaction review is recommended for anyone on three or more medications with a poor-or ultra-rapid-metabolizer CYP result before any addition (pharmacist-level review).

5. Timeline the patient will have read

The Kernel describes a 12-month arc. All dates and percentages below are **[Kernel hypothesis]** and are projections only.

Phase	Kernel timeframe	Kernel's stated expectations
Biological foundation	Months 1-3	Supplements titrated; sleep, energy, and brain fog improving; cravings "beginning to reduce (20- 40%)"
"Taper + support" Phase	Months 3-6 Kernel timeframe	Substance reduction after the foundation phase; cravings "reduced 40-70%" Kernel's stated expectations
Environmental redesign	Months 6-12	Exercise, sleep, and social environment reconfigured; supplements tapered as symptoms resolve

Phase	Kernel timeframe	Kernel's stated expectations
After year 1	Ongoing	Supplements stopped at symptom resolution, restarted if destabilized

Clinical cautions on this timeline.

- **Any substance or medication reduction is yours to direct.** The Kernel states that it defers taper decisions to prescribers, and the patient should not read "months 3-6" as an instruction.
- Do not allow the schedule to delay or stop opioid agonist treatment, or to postpone care of alcohol, benzodiazepine, Z-drug, GHB, or high-dose gabapentinoid dependence. Abrupt cessation of these can be dangerous; withdrawal must be medically supervised. The 2025 US Joint Clinical Practice Guideline on Benzodiazepine Tapering supports individualized tapering and treats a diazepam cross-taper as a prescriber's choice.
- **A break is not a reset.** Tolerance falls after any gap (relapse, incarceration, hospitalization); ensure naloxone access.

6. Kernel "expected outcomes" at about month 6

Kernel projections only. They are not trial results and the source gives no methodology. Scores are 1-10, intake to "homeostasis at month 6".

Depleted Worrier (MTHFR high + COMT	Understimulated Warrior (MTHFR high	GABRA2 high-risk (alcohol/benzodiazep

Measure	"Worrier")	+ COMT "Warrior")	ine pattern)
Mood stability	2 to 7	4 to 7	not listed
Energy	3 to 7	3 to 8	not listed
Anxiety (lower better)	8 to 3	not listed	9 to 3 (baseline)
Sleep quality	3 to 8	4 to 7	2 to 7 (without aids)
Craving intensity	8 to 2	7 to 2	"craving interruption" 1 to 6
Brain clarity or focus	3 to 8	3 to 8	not listed
Motivation / drive	not listed	2 to 7	not listed
Impulse control	not listed	not listed	2 to 6
Emotional regulation	not listed	not listed	2 to 7

The source notes early weeks “may show little change or temporary worsening”. Please treat all figures as hypothesis. In particular, a “Month 6” craving score of 2/10 is not an expected outcome for any individual, and a score that does not improve should not be framed as non- adherence.

7. Safety notes to keep in mind

- **Folic acid.** The Kernel advises replacing folic acid with L-methylfolate for patients with MTHFR T/T. **[Kernel hypothesis]** Mainstream guidance continues to recommend folic acid for neural-tube-defect prevention. Do not let this advice change prenatal or prescribed folate without your agreement.
- **Alcohol, benzodiazepine, Z-drug, and GHB withdrawal.** Any significant dependence needs medical supervision. GABRA2/GABRB3 results do not replace clinical risk assessment; prior withdrawal seizures or delirium are the clinical signal.
- **SAMe and bipolar disorder.** Contraindicated without a mood stabilizer (see table).
- **Serotonin syndrome.** Check for serotonergic combinations (SSRIs/SNRIs, MAOIs, tramadol, MDMA, 5-HTP, SAMe).
- **Psychosis.** Dopamine-raising supplements (such as tyrosine) should not be used while psychotic symptoms are active. Persistent perceptual symptoms warrant psychiatric evaluation.
- **CYP450 polypharmacy.** Three or more medications plus an abnormal-metabolizer result: pharmacist-level review before additions.
- **Smoking cessation.** Stopping smoking can raise levels of clozapine, olanzapine, and theophylline, and caffeine effects increase. Coordinate before the quit date.
- **Unverified supply.** Counterfeit pills can contain fentanyl, nitazenes, xylazine, and medetomidine. Naloxone does not reverse xylazine or medetomidine; nitazene overdoses may need repeated doses, and fentanyl test strips do not reliably detect nitazenes. Medetomidine withdrawal is a hospital-level problem.
- **Crisis resources for patients:** 911; 988 (call or text); Poison Control 1-800-222-1222; SAMHSA 1-800-662-4357; Crisis Text Line (text HOME to 741741).

8. Reasonable ways to respond

1. Ask what the patient is taking and why; record every supplement.
2. Review the list for interactions and contraindications before anything new.
3. Order tests only where they change management (for example CYP2D6 before codeine or tramadol; B12 and vitamin D for deficiency). Use clinical history for withdrawal and psychosis risk.
4. Keep evidence-based treatment intact and unhurried.

5. Treat a return to use as clinical information, with attention to tolerance and naloxone.
6. Make clear which parts of the Kernel you can support (sleep, nutrition, movement, structure, peer support) and which you cannot (genotype-guided addiction prediction, unproven supplement regimens, peptides). **Resources.** CPIC guidelines (cpicpgx.org); FDA Table of Pharmacogenomic Biomarkers in Drug Labeling (fda.gov); an interaction checker such as Drugs.com or Medscape. The Kernel is released into the public domain as a harm-reduction resource and is not a substitute for medical advice.

KEY POINTS

- The Kernel's outcome numbers are projections, not trial results.
- The best-supported genetic element is CYP2D6; most other claims are hypotheses.
- Supplement evidence is mechanism-based and mostly limited; doses are for you and the pharmacist.
- Keep the cautions: SAMe/bipolar, MAOIs and tyrosine, serotonergic combinations, psychosis, polypharmacy.
- Never let the timeline delay supervised treatment of dependence.